Pending Claims (after amendments and additions)

B1

59. A pharmaceutical composition comprising a therapeutically effective amount of an epothilone, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 mg to about 40 mg epothilone per kg body weight.

60. (Canceled)

B2

61. The composition of claim 59, further comprising at least one additional cytotoxic agent.

62. The composition of claim 61, wherein said at least one additional cytotoxic agent is an anti-cancer agent.

63. The composition of claim 62, wherein the anti-cancer agent is selected from the group consisting of adriamycin, vinblastin, and paclitaxel.

64. A method of treating cancer in a subject comprising:

administering a therapeutically effective amount of an epothilone to a subject in need thereof, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 mg to about 40 mg epothilone per kg body weight.

65. (Canceled)

B3

66. The method of claim 64, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.01 mg to about 40 mg epothilone per kg body weight.

67. The method of claim 64, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 to about 25 mg epothilone per kg body weight.

68. The method of claim 64, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.01 to about 25 mg epothilone per kg body weight.

69. The method of claim 64, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 to about 10 mg epothilone per kg body weight.

70. The method of claim 64, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.01 to about 10 mg epothilone per kg body weight.

71. The method of claim 64, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 to about 1 mg epothilone per kg body weight.

72. The method of claim 64, wherein the therapeutically effective amount of the epothilone is an amount sufficient to achieve deliver about 0.01 to about 1 mg epothilone per kg body weight.

73. The method of claim 64, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 25 mg or greater epothilone per kg body weight.

74. The method of claim 64, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 25 to about 40 mg epothilone per kg body weight.

75. The method of claim 64, wherein the therapeutically effective amount of the epothilone is effective to kill tumor cells or inhibit the growth of tumor cells.

76. The method of claim 75, wherein the tumor cells are a solid tumor.

77. The method of claim 75, wherein the tumor cells are selected from the group consisting of breast cancer cells, melanoma cells, leukemia cells, and ovarian cancer cells.

78. The method of claim 77, wherein the leukemia cells are myelocytic, lymphocytic, acute,

or chronic leukemic cells.

79. The method of claim 64, wherein the therapeutically effective amount of the epothilone is effective to kill multidrug resistant cells or inhibit the growth of multidrug resistant cells.

B4

80. A method of treating cancer in a subject comprising administering a therapeutically effective amount of a composition comprising an epothilone, wherein the therapeutically effective amount is an amount sufficient to deliver about 0.001 to about 40 mg epothilone per kg body weight.

81. (Canceled)

82. The method of claim 80, wherein said composition further comprises at least one additional cytotoxic agent.

B5

83. The method of claim 82, wherein said at least one additional cytotoxic agent is an anticancer agent.

84. The method of claim 83, wherein said anticancer agent is selected from the group consisting of adriamycin, vinblastin, and paclitaxel.

85. A method for treating paclitaxel-resistant cancer comprising:

administering a therapeutically effective amount of an epothilone to a subject in need thereof, wherein said therapeutically effective amount of said epothilone is sufficient to kill tumor cells resistant to paclitaxel or inhibit the growth of tumor cells resistant to paclitaxel; and

wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 to about 40 mg epothilone per kg body weight.

86. (Amended) A method for treating adriamycin-resistant cancer comprising:

administering a therapeutically effective amount of an epothilone to a subject in need

thereof, wherein said therapeutically effective amount of said epothilone is sufficient to kill tumor cells resistant to adriamycin or inhibit the growth of tumor cells resistant to adriamycin, and

wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 to about 40 mg epothilone per kg body weight.

B5 Cont'd

87. (Amended) A method of killing tumor cells or inhibiting the growth of tumor cells comprising:

contacting tumor cells with an amount of a composition comprising an epothilone, effective to kill tumor cells or inhibit the growth of tumor cells, wherein the amount of the epothilone is an amount sufficient to deliver about 0.001 to about 40 mg epothilone per kg body weight.

88. (Canceled)

B6

89. The method of claim 87, wherein said composition is administered in combination with at least one additional cytotoxic agent.

90. The method of claim 89, wherein said at least one additional cytotoxic agent is an anticancer agent.

91. The method of claim 90, wherein said anticancer agent is selected from the group consisting of adriamycin, vinblastin, and paclitaxel.

92. The method of claim 87, wherein the tumor cells are a solid tumor.

93. The method of claim 87, wherein the tumor cells are selected from the group consisting of breast cancer cells, melanoma cells, leukemia cells, and ovarian cancer cells.

94. The method of claim 93, wherein the leukemia cells are myelocytic, lymphocytic, acute

or chronic leukemic cells.

95. The method of claim 87, wherein the effective amount of the epothilone is effective to kill multidrug resistant cells or inhibit the growth of multidrug resistant cells.

96. A pharmaceutical composition for the treatment of cancer comprising:

a therapeutically effective amount of an epothilone, or pharmaceutically acceptable salts thereof; and

a pharmaceutically acceptable carrier or diluent,

wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 to about 40 mg epothilone per kg body weight of a subject.

97. The composition of claim 96, further comprising at least one additional cytotoxic agent.

98. The composition of claim 97, wherein said at least one additional cytotoxic agent is an anti-cancer agent.

99. The composition of claim 98, wherein the anti-cancer agent is selected from the group consisting of adriamycin, vinblastin, and paclitaxel.

100. The pharmaceutical composition of claim 96, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.01 to about 40 mg epothilone per kg body weight.

101. The pharmaceutical composition of claim 96, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 to about 25 mg epothilone per kg body weight.

102. The pharmaceutical composition of claim 96, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.01 to about 25 mg epothilone

anti-cancer agent.

99. The composition of claim 98, wherein the anti-cancer agent is selected from the group consisting of adriamycin, vinblastin, and paclitaxel.

100. The pharmaceutical composition of claim 96, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.01 to about 40 mg epothilone per kg body weight.

101. The pharmaceutical composition of claim 96, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 to about 25 mg epothilone per kg body weight.

102. The pharmaceutical composition of claim 96, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.01 to about 25 mg epothilone per kg body weight.

103. The pharmaceutical composition of claim 96, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 to about 10 mg epothilone per kg body weight.

104. The pharmaceutical composition of claim 96, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.01 to about 10 mg epothilone per kg body weight.

105. The pharmaceutical composition of claim 96, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 to about 1 mg epothilone per kg body weight.

106. The pharmaceutical composition of claim 96, wherein the therapeutically effective

amount of the epothilone is an amount sufficient to deliver of about 0.01 to about 1 mg epothilone per kg body weight.

107. A pharmaceutical composition for the treatment of cancer comprising:

a therapeutically effective amount of an epothilone, or pharmaceutically acceptable salts thereof; and

a pharmaceutically acceptable carrier or diluent,

wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.01 mg to about 10 mg epothilone per kg body weight of a subject.

108. A pharmaceutical composition comprising a therapeutically effective amount of an epothilone macrolide, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.01 to about 10 mg epothilone per kg body weight of a subject.

109. A method of treating cancer in a subject comprising:

administering a therapeutically effective amount of an epothilone to a subject in need thereof, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver of about 0.01 to about 10 mg epothilone per kg body weight.

110. A method of treating cancer in a human comprising:

administering a therapeutically effective amount of an epothilone to a subject in need thereof, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.01 to about 10 mg epothilone per kg body weight.

111. The method of claim 64, wherein the step of administering comprises administering multiple times a therapeutically effective amount of an epothilone to a subject in need thereof, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 mg to about 40 mg epothilone per kg body weight.

112. The method of claim 80, wherein the step of administering comprises administering multiple times a therapeutically effective amount of a composition comprising an epothilone, wherein the therapeutically effective amount is an amount sufficient to deliver about 0.001 to about 40 mg epothilone per kg body weight.

113. The method of claim 64, wherein the step of administering comprises administering multiple times a therapeutically effective amount of an epothilone to a subject in need thereof, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver of about 0.01 to about 10 mg epothilone per kg body weight.

114. The method of claim 80, wherein the step of administering comprises administering multiple times a therapeutically effective amount of a composition comprising an epothilone, wherein the therapeutically effective amount is an amount sufficient to deliver about 0.01 to about 10 mg epothilone per kg body weight.

115. The method of claim 85, wherein the step of administering comprises:

administering multiple times a therapeutically effective amount of an epothilone to a subject in need thereof, wherein said therapeutically effective amount of said epothilone is sufficient to kill tumor cells resistant to paclitaxel or inhibit the growth of tumor cells resistant to paclitaxel; and

wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 to about 40 mg epothilone per kg body weight.

116. The method of claim 86, wherein the step of administering comprises:

administering multiple times a therapeutically effective amount of an epothilone to a subject in need thereof, wherein said therapeutically effective amount of said epothilone is sufficient to kill tumor cells resistant to adriamycin or inhibit the growth of tumor cells resistant to adriamycin, and

wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 to about 40 mg epothilone per kg body weight.

117. The method of claim 64, wherein the step of administering comprises:

administering in multiple doses a therapeutically effective amount of an epothilone to a subject in need thereof, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 mg to about 40 mg epothilone per kg body weight.

118. The method of claim 80, wherein the step of administering comprises:

administering in multiple doses a therapeutically effective amount of a composition comprising an epothilone, wherein the therapeutically effective amount is an amount sufficient to deliver about 0.001 to about 40 mg epothilone per kg body weight.

119. The method of claim 64, wherein the step of administering comprises:

administering in multiple doses a therapeutically effective amount of an epothilone to a subject in need thereof, wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver of about 0.01 to about 10 mg epothilone per kg body weight.

120. The method of claim 80, wherein the step of administering comprises:

administering in multiple doses a therapeutically effective amount of a composition comprising an epothilone, wherein the therapeutically effective amount is an amount sufficient to deliver about 0.01 to about 10 mg epothilone per kg body weight.

121. The method of claim 85, wherein the step of administering comprises:

administering in multiple doses a therapeutically effective amount of an epothilone to a subject in need thereof, wherein said therapeutically effective amount of said epothilone is sufficient to kill tumor cells resistant to paclitaxel or inhibit the growth of tumor cells resistant to paclitaxel; and

wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 to about 40 mg epothilone per kg body weight.

122. The method of 86, wherein the step of administering comprises:

administering in multiple doses a therapeutically effective amount of an epothilone to a subject in need thereof, wherein said therapeutically effective amount of said epothilone is sufficient to kill tumor cells resistant to adriamycin or inhibit the growth of tumor cells resistant to adriamycin, and

wherein the therapeutically effective amount of the epothilone is an amount sufficient to deliver about 0.001 to about 40 mg epothilone per kg body weight.--

III. Rejection of claims 87-95 under 35 U.S.C. § 112, first and second paragraphs:

The Examiner has rejected claims 87-95 under 35 U.S.C. § 112, first paragraph and asserts that the specification, while being enabling for inducing apoptosis (cell death) of cancer or tumor cells, does not reasonably provide enablement for their inhibition. The Examiner states that if the term "inhibition" is deleted, that the rejection would be overcome. The Examiner has also rejected claims 87-95 under 35 U.S.C. § 112, second paragraph and asserts that the term "killing" is indefinite because it is not consistent with induction of apoptosis by epothilones. The Examiner states that if the term "killing" is replaced with "apoptosis" the rejection would be overcome. Applicant disagrees that pending claims 87-95 are not enabled by the present application, and respectfully traverses the rejection.

Applicant appreciates and acknowledges Examiner's point that the mechanism by which epothiolones kill cells or inhibit cell growth may involve induction of apoptosis. However, Applicant respectfully submits that the mechanism by which epothilones act is not material to the question of enablement. The present specification provides ample evidence that epothilones A and B, as well as other epothilones, are capable of killing cells or inhibiting the growth of various tumor cells lines (see, for example, pp. 63-87; Tables 5 and 7). In addition, the specification includes data (*e.g.*, Tables 11, 12, and 13) from several mouse models of cancer, in which epothilone B has been administered and shown to decrease the tumor volume. The specification is therefore fully supportive of claims to methods of killing tumor cells or inhibiting tumor cell growth. Applicant respectfully submits that the rejection of claims 87-95 for lack of enablement should be removed.

The Examiner also rejected claim 63 for lack of proper antecedent basis in claim 59. Applicant thanks the Examiner for pointing out the improper dependency of this claim, which

has been amended to depend instead from claim 62.

IV. Rejection of claims 30 and 59-94 under 35 U.S.C. § 103(a):

The Examiner has rejected claims 59-95 under 35 U.S.C. § 103(a) as being unpatentable over the Bollag *et al.* reference (*Cancer Res.*, Vol. 55 (1995), pages 2325-2333). The Examiner asserts that the Bollag *et al.* reference teaches "epothilones A and B, their compositions as an oily residue (column 2, page 2326) and methods of use for treating cancer or tumor cells and particularly multiple drug-resistant cells. (See column 2, page 2331)." The Examiner further asserts that the Bollag *et al.* reference teaches "the method of use of epothilones in combination with taxol (a cytotoxic agent). See column 2, page 2328 to column 1, page 2330." In the section entitled "Ascertainment of the difference between the prior art and the claims" the Examiner states that "the difference between the instant invention and the disclosure of Bollag *et al.*, is that applicants are claiming effective amounts of epothilones from 0.001 to 40 mg/kg of body weight." In the section labeled "Finding of *prima facie* obviousness—rational and motivation" the Examiner then asserts that "for the Bollag *et al.*, to use epothilones for the treatment of cancer or tumors, effective amount must necessarily be used," and states that Applicant's "claiming effective amounts of epothilones from 0.001 to 40 mg/kg of body weight, is not in and of itself patentable over the prior art of Bollag *et al.*" The Examiner further states that "the motivation is to make additional epothilone compositions useful for the treatment of cancer."

Applicant respectfully submits that the Examiner does not establish a *prima facie* case of obviousness based on the Bollag *et al.* reference. In particular, Applicant respectfully submits that the reference by Bollag *et al.* does not teach the preparation or use of compositions comprising *therapeutically effective amounts* of epothilones in treating cancer. At most, Bollag *et al.* might be said to provide motivation to try to prepare and use such compositions, but there can be no reasonable expectation of success based on the teachings of Bollag *et al.*

See action from 09/574

The teachings of Bollag *et al.* are very limited. Bollag *et al.* teach epothilones purified from a natural source, *Sorangium cellulosum*, and therefore, are necessarily limited to epothilones A and B, the two epothilones produced by the organism. Bollag *et al.* does not teach or suggest derivitization and modification of the isolated epothilones A and B. By contrast, the present application teaches a variety of different epothilone compounds, and provides a synthetic

No matter the source epos A+B would always be the same

strategy that, as indicated, allows ready introduction of certain structural modifications and derivatization to produce a wide array of epothilones beyond epothilones A and B. Bollag *et al.* does not teach or suggest any such structural variations; its teachings are absolutely limited to epothilones A and B.

Furthermore, because the Bollag *et al.* reference describes the testing of epothilones A and B only in *in vitro* assays (*i.e.*, to evaluate their effects on tubulin polymerization and growth inhibition in cell culture), Bollag *et al.* cannot teach or suggest a pharmaceutical composition comprising a therapeutically effective composition even of epothilones A and B. The reference itself acknowledges that results in such *in vitro* studies often do not correlate with *in vivo* activities (p. 2332, column 2). Bollag *et al.* do not provide any evidence that epothilones A and B will work to inhibit cell growth or kill cells *in vivo* such as in an established animal model for cancer. By contrast, the present application provides evidence in the form of data from well-established mouse models for cancer demonstrating that epothilone B (see tables 8, 12, and 13), as well as other epothilones, are useful in the treatment of cancer. Applicant therefore provided the first demonstration in an established animal cancer model that pharmaceutical compositions comprising a therapeutically effective amount of an epothilone are effective in killing tumor cells and inhibiting the growth of tumor cells. Moreover, Applicant discovered the novel and non-obvious therapeutically effective dose ranges to achieve the desired anti-cancer effect in an animal. The Bollag *et al.* reference does not disclose or suggest the ranges claimed by Applicant and therefore does not provide a basis for rejecting claims containing those ranges under 35 U.S.C. § 103.

Bollag *et al.* particularly fails to teach compositions comprising an amount of epothilone sufficient to deliver between 0.001 to 40 mg epothilone per kg body weight. Bollag *et al.* only teach amounts of epothilone A and B useful in mitotic arrest studies (*e.g.*, 10^{-7}-10^{-9} M), cytotoxicity studies (*e.g.*, 10^{-7}-10^{-9} M), and microtubule polymerization studies (*e.g.*, 10^{-6}-10^{-9} M), and Bollag *et al.* do *not* teach amounts useful *in vivo*. With regard to *in vivo* use, Bollag *et al.* even state in their Discussion section that "many agents identified as potent agonists or antagonists of *in vitro* activity in drug screening can prove to have secondary activities that limit their usefulness *in vivo*," (p. 2332, col. 2), thereby, acknowledging that their own assays may not be able to identify doses that are effective, since such assays fail to identify side effects or other

deficiencies of a composition that are seen when it is tested in a whole organism. In contrast, the present specification, which includes experimental evidence from *in vivo* mouse studies supporting the claimed invention, demonstrates the effectiveness of compositions that deliver amounts of epothilone ranging between 0.001 and 40 mg epothilone per kg body weight (see tables 8-18, pages 75-87), as recited in the present claims.

Furthermore, the Bollag *et al* reference itself actually *teaches away* from the desirability of formulating pharmaceutical compositions from epothilones A or B. The reference indicates that Bollag *et al.* considered epothilones A and B to be lead compounds that, once derivatized, might provide the basis for a therapeutic composition. For instance, in the Introduction to the paper, Bollag *et al.* identify their desire to find a novel class of MT-stabilizing drugs that "*might stimulate* the development of more effective cancer chemotherapeutics with this mechanism of action." (p. 2325, col. 1). Similarly, in the Conclusion section, the authors state "the simpler chemical structure of epothilones may instead provide a *useful lead compound in the quest for a drug* operating by the same mechanism MT-stabilizing mechanism as taxol" (p. 2333, col. 1). These statements indicate that Bollag *et al.* themselves did not consider epothilones A and B to be appropriate components of a pharmaceutical compositions; rather they considered these compounds to be starting points in the pursuit of an appropriate therapeutically effective entity.

For all the reasons set forth above, the claimed pharmaceutical compositions and methods of treating cancer cannot be rendered obvious by the limited teachings of Bollag *et al.*

V. Provisional Double Patenting Rejection:

The Examiner has provisionally rejected claims 59-95 under 35 U.S.C. § 101 as claiming the same invention as that of claims 30 and 59-94 of co-pending application number 09/874,514 (the '514 application).

As stated in MPEP 804, "same invention" means identical subject matter. *See Miller v. Eagle Mfg. Co.* 151 US 186 (1984); *In re Vogel*, 422 F. 2d 438, 164 USPQ 619 (CCPA 1970); and *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957). Applicants respectfully submit that claims 59-95 of the present application cover the genus of epothilone compounds, whereas each of the claims of U.S.S.N. 09/874,514 (claims 30 and 59-94) covers a specific subgenus or species of epothilone compounds. Thus, Applicant respectfully submits that identical subject

matter is not defined by both sets of claims and statutory double patenting does not exist.

Furthermore, and solely to expedite allowance of this application, Applicant submits herewith a terminal disclaimer. The terminal disclaimer disclaims any portion of the term of a patent that issues from this application that extends beyond a patent that issues from USSN 09/784,514. Applicant submits that the terminal disclaimer submitted herewith removes any basis for an obviousness-type double patenting rejection based on the latter application.

In view of the remarks provided above, Applicant respectfully requests that the provisional statutory double patenting rejection be withdrawn and that the claims be allowed without further delay.

VI. Objection:

The Examiner has objected to claims 59 and 60 and asserts that they are duplicates because claim 59 is drawn to a composition that inherently must comprise a pharmaceutically acceptable carrier or diluent. To expedite prosecution, Applicant has canceled without prejudice claim 60 (and claims 81 and 88) and thus respectfully requests that the rejection be withdrawn.

VII. Specification:

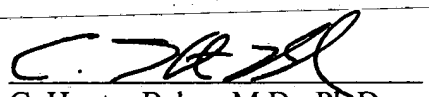
The Examiner has indicated that pages 76 and 86 of the specification are missing the last 1-2 lines. Applicant has provided replacement pages for pages 76 and 86 herewith that include the last 1-2 lines.

VIII. Information Disclosure:

Applicant has provided herewith a modified PTO 1449 form citing a U.S. patent application (US 2002/0028839) published on March 7, 2002, entitled "Cancer Treatment with Epothilones". The earliest priority date of this application (resulting from GB application number 9803907.6) is February 25, 1998, which date is *after* the actual filing date of Applicant's priority patent application (08/986,025, filed December 3, 1997, now U.S. Patent 6,242,469, the earliest priority date of which results from U.S. provisional application number 60/032,282, filed December 3, 1996).

If it is believed that a telephone conversation would expedite matters, the Examiner is invited to contact the undersigned at (617) 248-5215. The Examiner's attention is also directed to the recent change in power of attorney and correspondence address, as submitted herewith. Although it is believed that there is no fee associated with this amendment, if Applicant is mistaken, please charge any fees to our Deposit Account No.: 03-1721.

Respectfully Submitted,



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